Access DB# 97057

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name Jeffrey Russel Examiner #: 62785 Date: 6-19-2003

Art Unit 1654 Phone Number 308-3975 Serial Number 09/830,741

Mail Box and Bldg Room Location CM1-11D13/CM1-7807 Results Format Preferred (circle) PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Phosphinate peptide analogs for the treatment of fibrotic disorders

Inventors (please provide full names): E. Burchardt, M. Schauer, W. Stocker, T. Lampe

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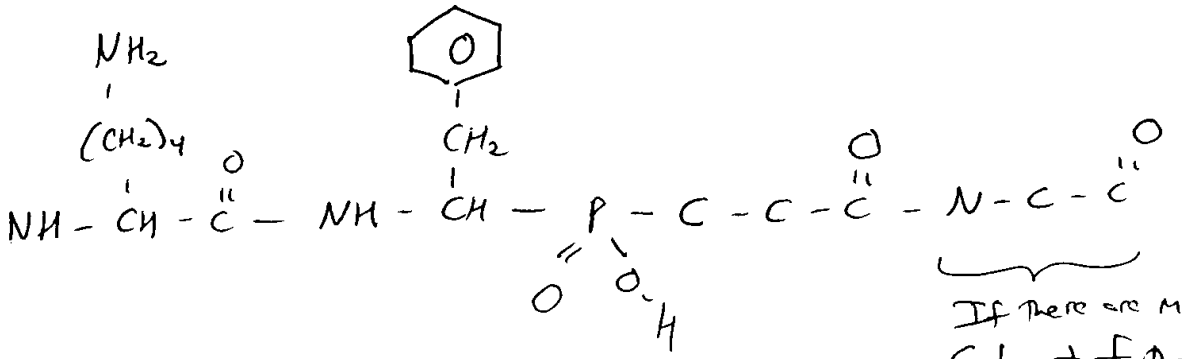
Earliest Priority Filing Date: 4-30-2001

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search the following partial structure:



If there are many hits on the first part of the structure, please add this residue.

If necessary please use the keywords fibro?, pcp, procollagen, laminin, collagen.

Thank you.

JR

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=> d que
L1                 STR
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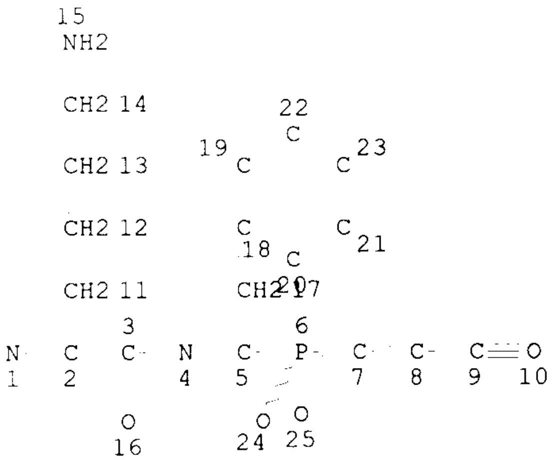


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NODE ATTRIBUTES:
CONNECT IS E3  RC AT   2
CONNECT IS E2  RC AT   4
CONNECT IS E3  RC AT   5
CONNECT IS E1  RC AT  24
CONNECT IS E1  RC AT  25
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L3            33 SEA FILE=REGISTRY SSS FUL L1
L4             8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L5             3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND (FIBRO? OR PCP OR
                 PROCOLLAGEN OR LAMININ OR COLLAGEN)
L6             8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR L5


=> d ibib abs hitstr l6 1-8
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L6 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:76639 HCAPLUS

DOCUMENT NUMBER: 138:131168

TITLE: Phosphinate-peptide analogues as inhibitors of **procollagen** C-proteinase (**pcp**) for treating **fibrotic** diseases

INVENTOR(S): Burchardt, Elmar Reinhold; Stocker, Walter

PATENT ASSIGNEE(S): Germany

SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007980	A1	20030130	WO 2002-DE2583	20020713

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10134243	A1	20030327	DE 2001-10134243	20010714

PRIORITY APPLN. INFO.: DE 2001-10134243 A 20010714

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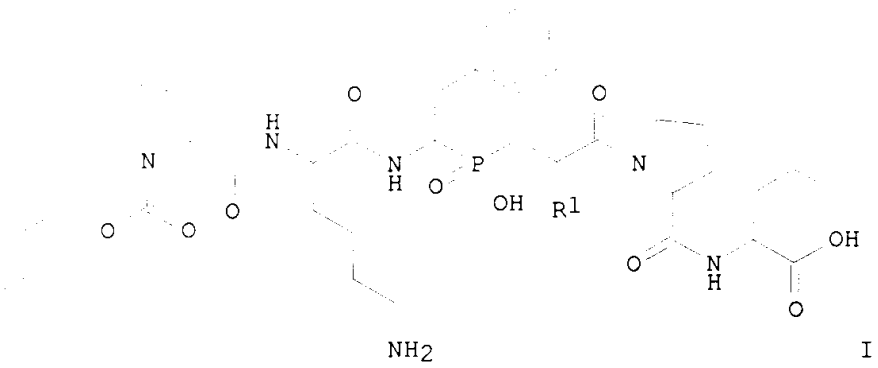


I

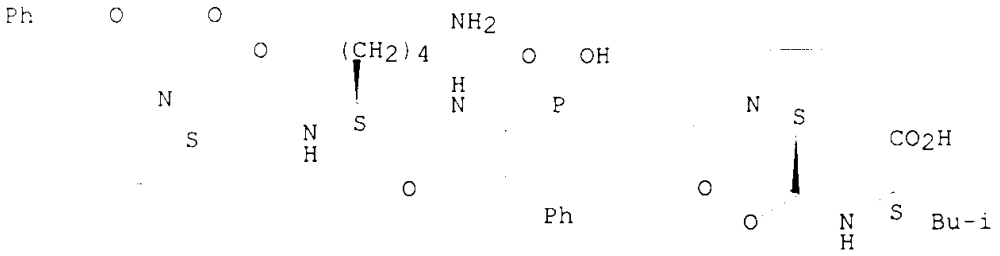
AB The invention discloses the use of phosphinate-peptide analogs I (R1 = H, Me) as inhibitors of **procollagen** C-proteinase, for treating **fibrotic** diseases.

IT **489412-73-9 489412-73-9D**, stereoisomers
489412-74-0 489412-74-0D, stereoisomers
489412-75-1 489412-75-1D, stereoisomers
489412-76-2 489412-76-2D, stereoisomers
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphinate-peptide analogs as inhibitors of **procollagen** C-proteinase (**pcp**) for treating **fibrotic** diseases)

RN 489412-73-9 HCAPLUS

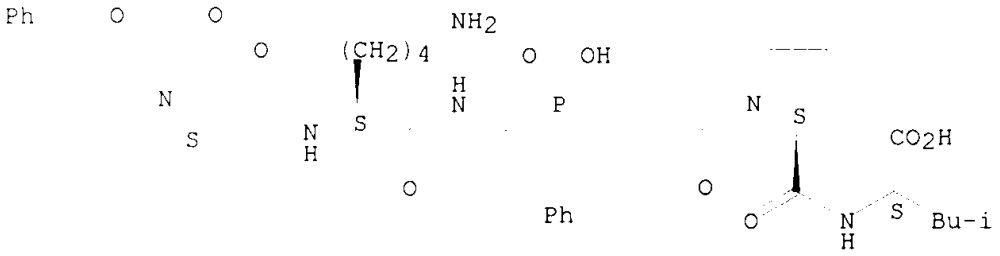
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



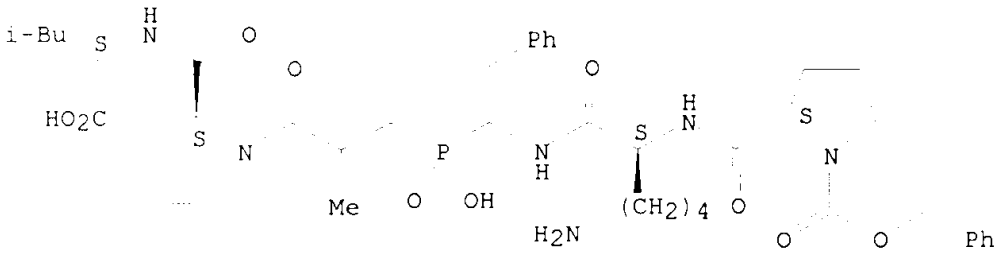
RN 489412-73-9 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



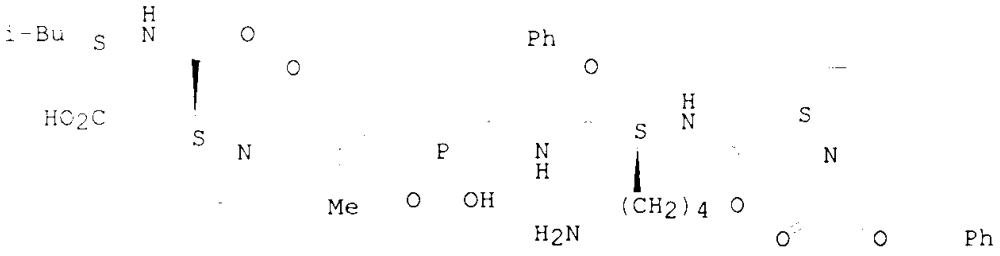
RN 489412-74-0 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



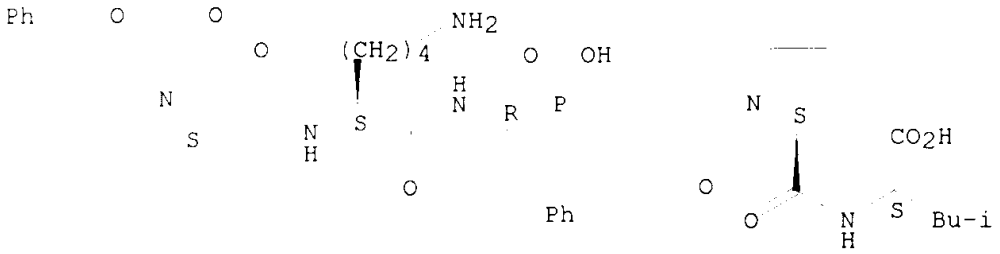
RN 489412-74-0 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



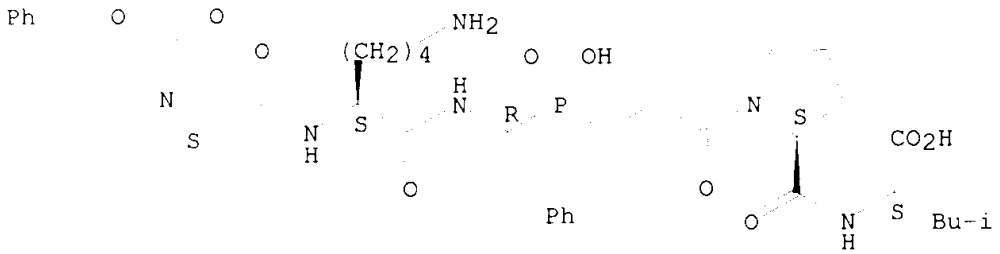
RN 489412-75-1 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 489412-75-1 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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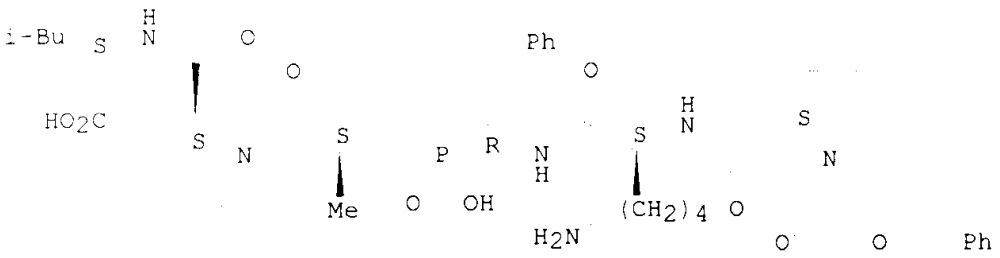
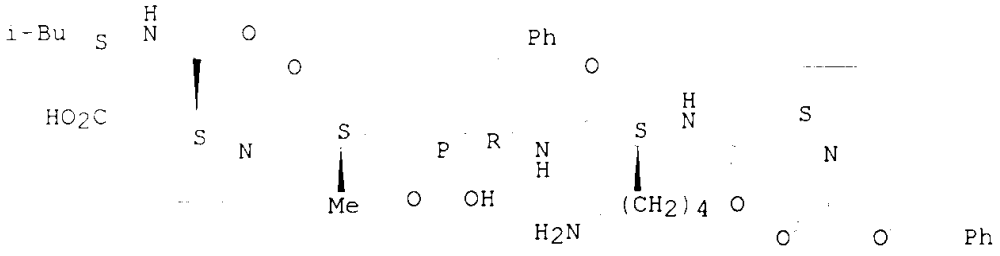
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-.psi.(PO(OH)-CH2)-L-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 489412-76-2 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-.psi.(PO(OH)-CH2)-L-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:289131 HCAPLUS
DOCUMENT NUMBER: 132:303510
TITLE: Phosphinate peptide analogs for the treatment of **fibrotic** disease
INVENTOR(S): Burchardt, Elmar-Reinhold; Schauer, Michael; Stocker, Walter
PATENT ASSIGNEE(S): Bayer A.-G., Germany
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19850072	A1	20000504	DE 1998-19850072	19981030
WO 2000027377	A2	20000518	WO 1999-EP8181	19991028
WO 2000027377	A3	20001116		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1124845 A2 20010822 EP 1999-969897 19991028

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002529403 T2 20020910 JP 2000-580606 19991028

PRIORITY APPLN. INFO.: DE 1998-19850072 A 19981030

WO 1999-EP8181 W 19991028

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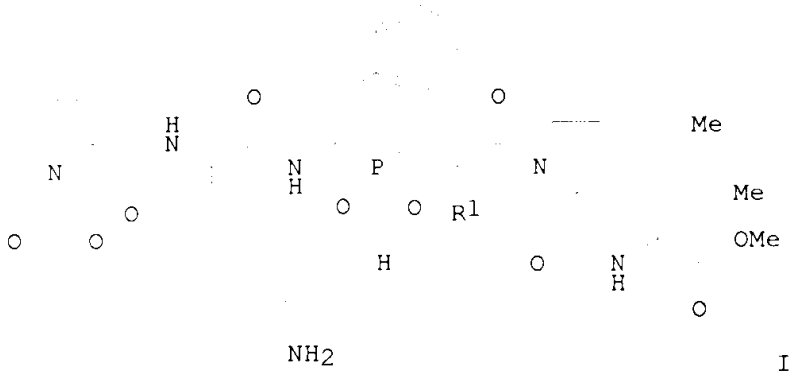


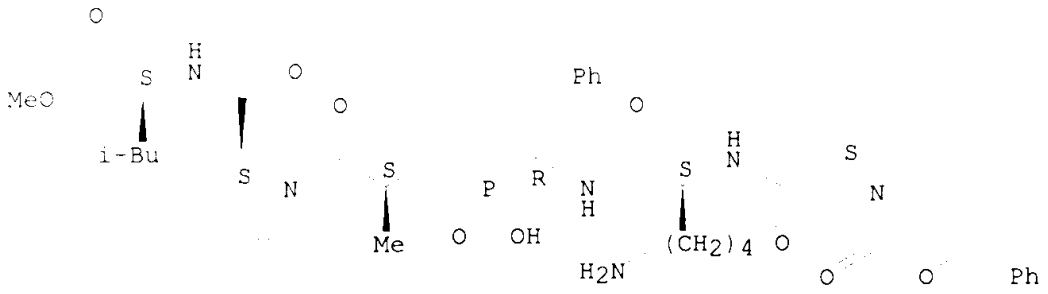
AB Phosphinate peptide analogs I (R1 = H, Me) are disclosed as inhibitors of **procollagen** C proteinase for the treatment of **fibrotic** disease, e.g. liver **fibrosis**.

IT **209247-63-2 209247-63-2D**, stereoisomers
209247-69-8 209247-69-8D, stereoisomers
265979-02-0 265979-02-0D, stereoisomers
265979-03-1 265979-03-1D, stereoisomers
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphinate peptide analogs for the treatment of **fibrotic** disease)

RN 209247-63-2 HCAPLUS

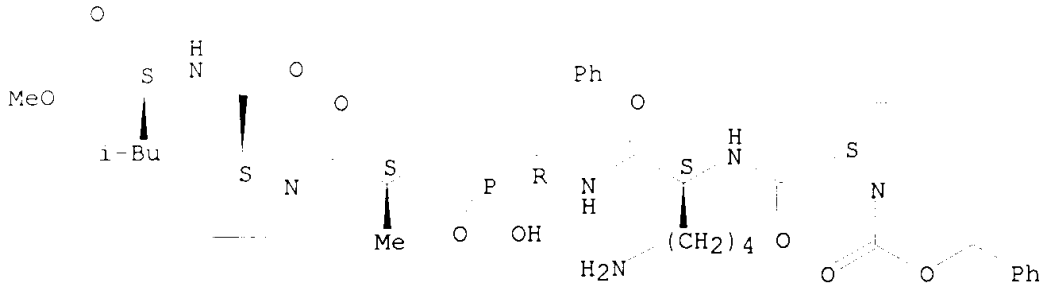
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 209247-63-2 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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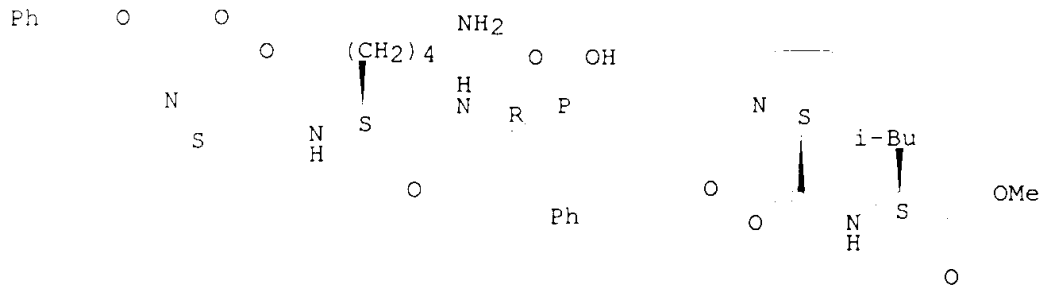
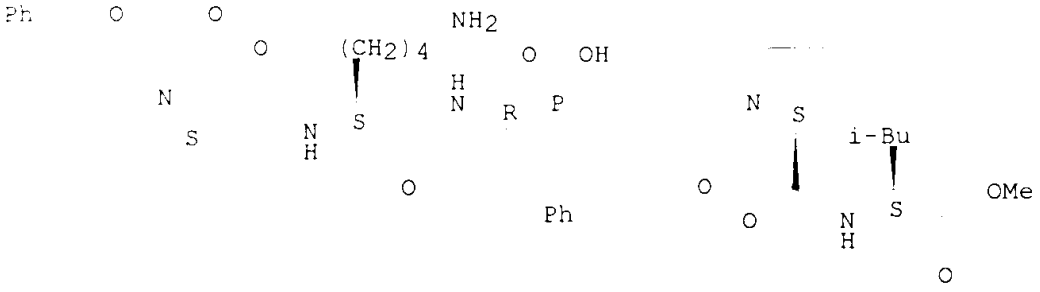
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 209247-69-8 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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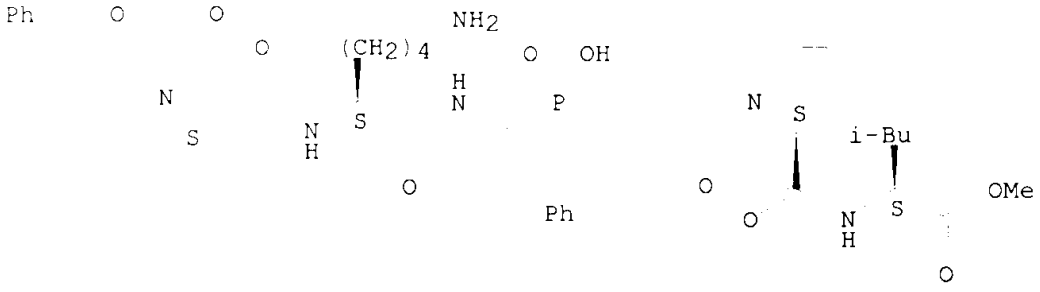
Absolute stereochemistry.



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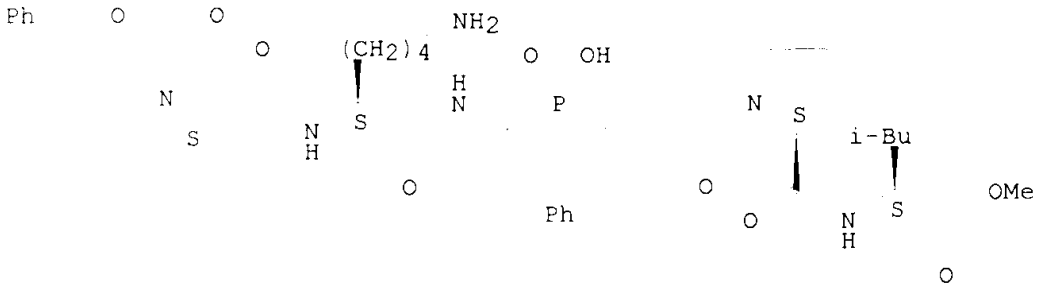
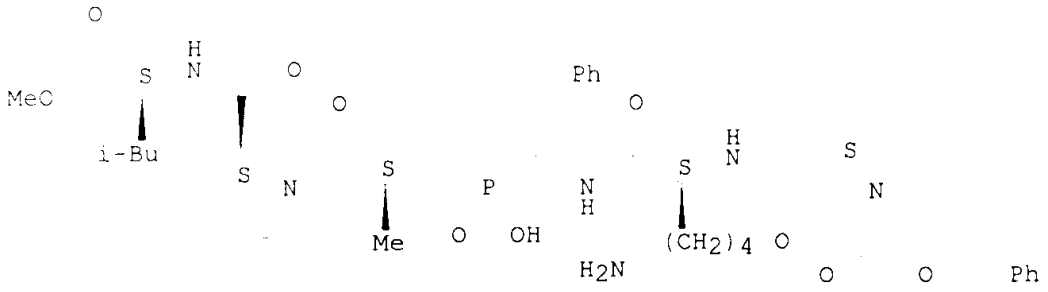
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[(1-amino-2-phenylethyl)hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



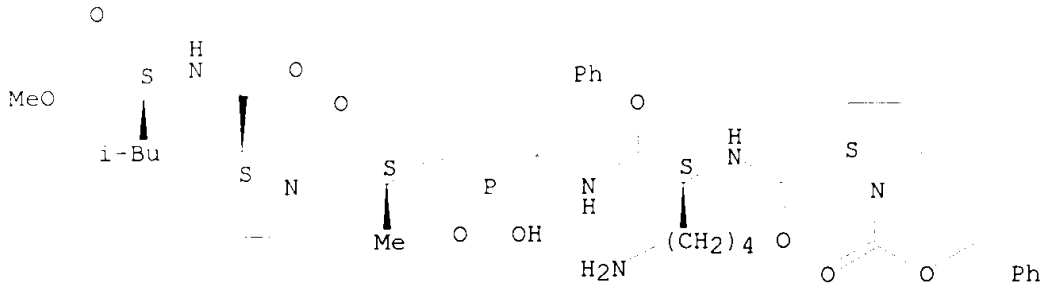
RN 265979-03-1 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[(1-amino-2-phenylethyl)hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 265979-03-1 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[(1-amino-2-phenylethyl)hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



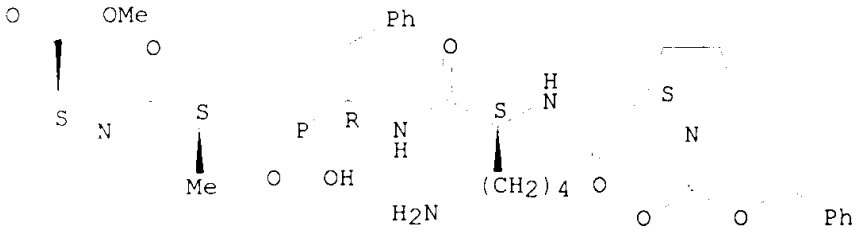
L6 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:289115 HCAPLUS
DOCUMENT NUMBER: 129:78349
TITLE: Phosphinic peptides, the first potent inhibitors of astacin, behave as extremely slow-binding inhibitors
AUTHOR(S): Yiallouros, Irene; Vassiliou, Stamatia; Yiotakis, Athanasios; Zwilling, Robert; Stocker, Walter; Dive, Vincent
CORPORATE SOURCE: Zoologisches Institut der Universitat Heidelberg, Physiologie, Heidelberg, D-69120, Germany
SOURCE: Biochemical Journal (1998), 331(2), 375-379
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of phosphinic pseudo-peptides varying in length and compn. have been designed as inhibitors of the crayfish zinc endopeptidase astacin, the prototype of the astacin family and of the metzincin superfamily of metalloproteinases. The most efficient phosphinic peptide, fluorenylmethyloxycarbonyl-Pro-Lys-Phe.psi.(PO2CH2)Ala-Pro-Leu-Val, binds to astacin with a Ki value of 42 nM, which is about three orders of magnitude below the corresponding values for previously used hydroxamic acid derivs. However, the rate consts. for assocn. (kon = 96.8 M-1 s-1) and dissocn. (koff = 4.1 .times. 10-6 s-1) are evidence for the extremely slow binding behavior of this compd. N-terminally or C-terminally

truncated phosphinic analogs of this parent mol. are much less potent, indicating a crit. role of the peptide size on the potency. In particular, omission of the N-terminal proline residue leads to a 40-fold increase in Ki which is mostly due to a 75-fold higher koff value. These findings are consistent with the previously solved crystal structure of astacin complexed with one of the phosphinic peptides, benzyloxycarbonyl-Pro-Lys-Phe.psi.(PO2CH2)Ala-Pro-O-Me, Ki = 14 .mu.M [Grams, Dive, Yiotakis, Yiallouros, Vassiliou, Zwilling, Bode and Stocker (1996) Nature Struct. Biol. 3, 671-675]. This structure also reveals that the phosphinic group binds to the active site as a transition-state analog. The extremely slow binding behavior of the phosphinic peptides is discussed in the light of the conformational changes involving a unique tyrosine switch in the structure of astacin upon inhibitor binding. The phosphinic peptides may provide a rational basis for the design of drugs directed toward other members of the astacin family which, like bone morphogenetic protein 1 (BMP1; i.e. the **procollagen** C-proteinase), have become targets of pharmacol. research.

IT **209247-62-1 209247-63-2 209247-64-3**
209247-65-4 209247-68-7 209247-69-8
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(phosphinic peptides, the first potent inhibitors of astacin, behave as extremely slow-binding inhibitors)

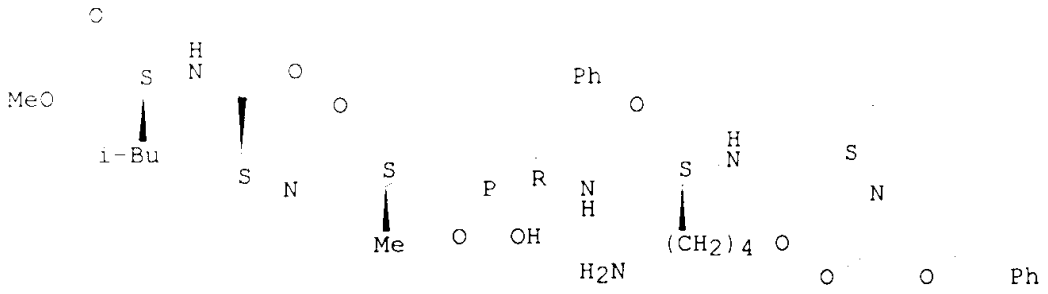
RN 209247-62-1 HCAPLUS
CN L-Proline, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 209247-63-2 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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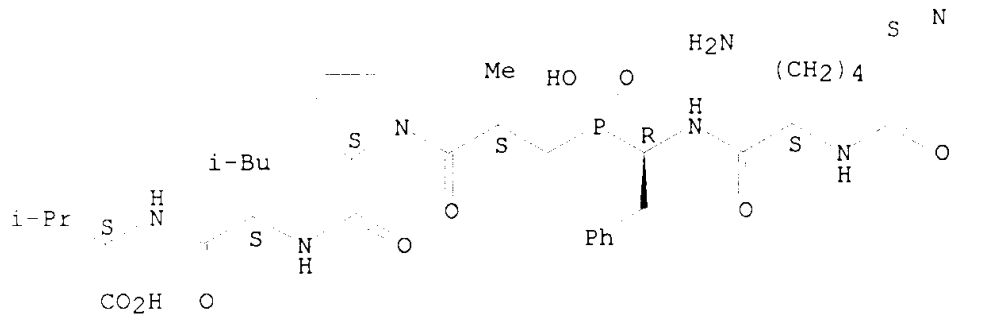
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

RN 209247-65-4 HCAPLUS
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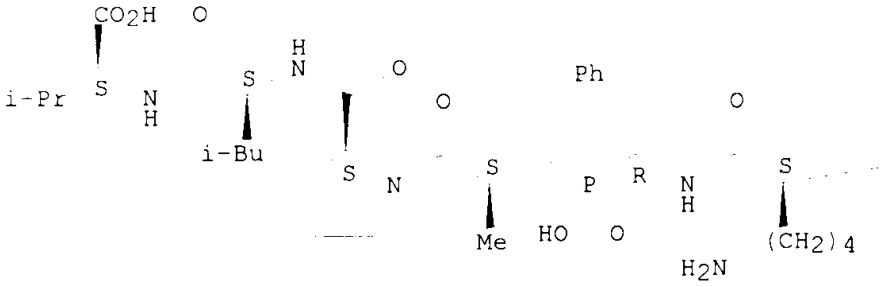
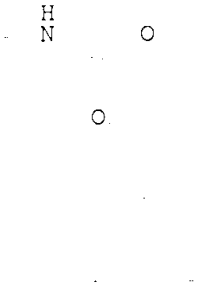
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

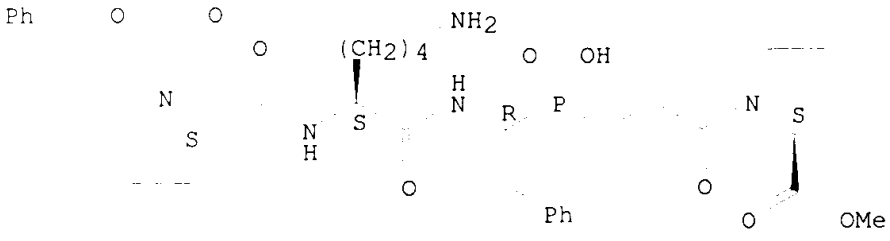


PAGE 1-B



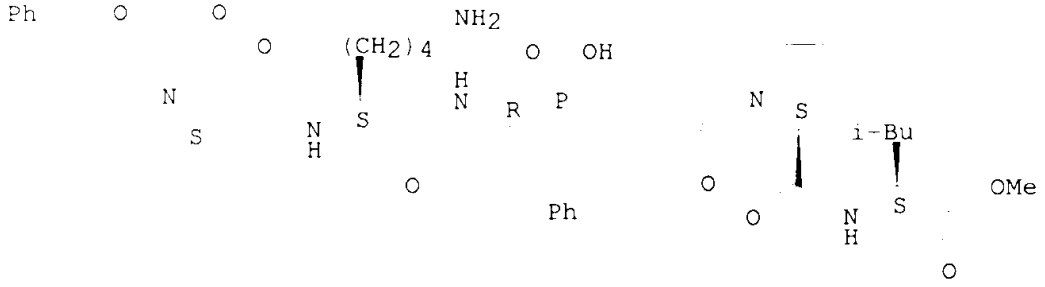
RN 209247-68-7 HCAPLUS
CN L-Proline, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 209247-69-8 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

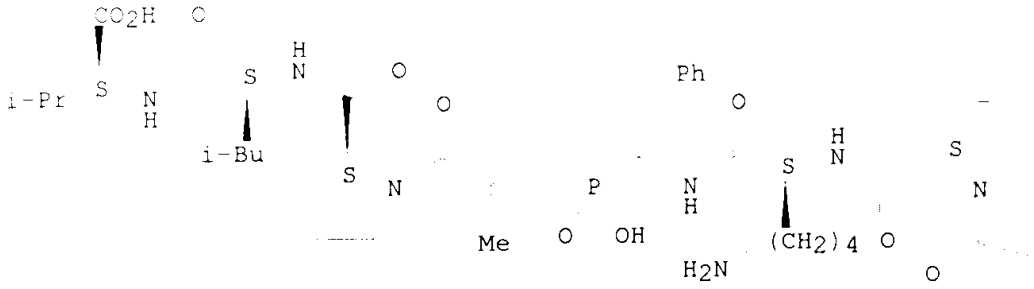


REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:531753 HCAPLUS
DOCUMENT NUMBER: 125:248435
TITLE: Protection of the Hydroxyphosphinyl Function of Phosphinic Dipeptides by Adamantyl. Application to the Solid-Phase Synthesis of Phosphinic Peptides
AUTHOR(S): Yiotakis, Athanasios; Vassiliou, Stamatia; Jiracek, Jiri; Dive, Vincent
CORPORATE SOURCE: Department of Organic Chemistry, University of Athens, Athens, 15771, Greece
SOURCE: Journal of Organic Chemistry (1996), 61(19), 6601-6605
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To develop solid-phase synthesis of phosphinic peptides, different FmocXaa.PSI.[PO(OAd)CH2]XaaOH [Fmoc = (fluorenylmethoxy)carbonyl, Ad = 1-adamantyl] building blocks have been prepd. In this respect, the protection of the hydroxyphosphinyl function in these phosphinic dipeptides by the adamantyl group turns out to be convenient. The phosphinic adamantyl esters are completely stable under basic conditions and can be removed under relatively mild acidic conditions. Using these building blocks, despite the bulkiness of the adamantyl group, no particular problem of coupling was obsd. during the solid-phase synthesis of phosphinic peptides by the Fmoc strategy. The developed methodol. is of particular interest to facilitate the development of potent inhibitors of zinc-metallo proteases.
IT **182193-50-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(solid-phase synthesis of phosphinic peptides)
RN 182193-50-6 HCAPLUS
CN L-Valine, N-[N-[1-[3-[hydroxy[2-phenyl-1-[[N2-[1-[(phenylmethoxy)carbonyl]-L-prolyl]-L-lysyl]amino]ethyl]phosphinyl]-2-methyl-1-oxopropyl]-L-prolyl]-L-leucyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

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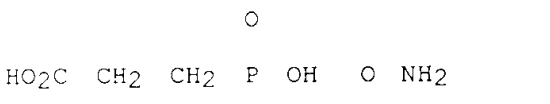
L6 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:498583 HCAPLUS
DOCUMENT NUMBER: 125:189128
TITLE: Development of the first potent and selective inhibitor of the zinc endopeptidase neurolysin using a systematic approach based on combinatorial chemistry of phosphinic peptides
AUTHOR(S): Jiracek, Jiri; Yiotakis, Athanasios; Vincent, Bruno; Checler, Frederic; Dive, Vincent
CORPORATE SOURCE: Departement d'Ingenierie et d'Etudes des Proteines, Commissariat a l'Energie Atomique, Gif-sur-Yvette, Fr.
SOURCE: Journal of Biological Chemistry (1996), 271(32), 19606-19611
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new systematic approach, based on combinatorial chem. of phosphinic peptides, is proposed for rapid development of highly potent and selective inhibitors of zinc metalloproteases. This strategy first evaluates the effects on the inhibitory potency and selectivity of the following parameters: (1) size of the phosphinic peptides, (2) position of the phosphinic bond in the sequence, and (3) the state (free or blocked) of the peptide extremities. After this selection step, the influence of the

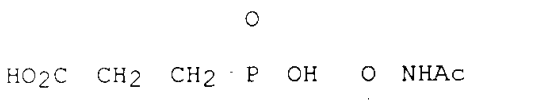
inhibitor sequence is analyzed to det. the identity of the residues that optimized both the potency and the selectivity. We demonstrate the efficiency of this novel approach in rapid identification of the first potent inhibitor of the mammalian zinc endopeptidase neurolysin (24-16), able to discriminate between this enzyme and the related zinc endopeptidase thimet oligopeptidase (24-15). The most potent and selective inhibitor developed in this study, Pro-LPhe.psi.(PO2CH2)Gly-Pro, displays a Ki value of 4 nM for 24-16 and is 2000 times less potent on 24-15. The specific recognition of such a free phosphinic tetrapeptide by 24-16, as well as the unique specificity of the 24-16 S2 and S2' subsites for proline, unveiled by this study, are discussed in terms of their possible significance for the function of this enzyme and its related zinc endopeptidase activities.

IT **181111-15-9 181111-35-3 181111-55-7 181111-75-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(development of the first potent and selective inhibitor of the zinc endopeptidase neurolysin using a systematic approach based on combinatorial chem. of phosphinic peptides)

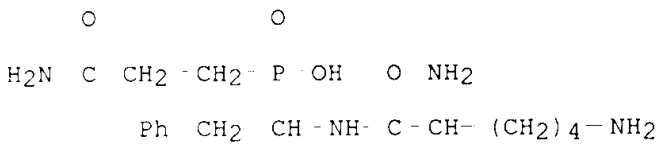
RN 181111-15-9 HCAPLUS
CN Propanoic acid, 3-[[1-[(2,6-diamino-1-oxohexyl)amino]-2-phenylethyl]hydroxyphosphinyl]- (9CI) (CA INDEX NAME)



RN 181111-35-3 HCAPLUS
CN Propanoic acid, 3-[[1-[[2-(acetylamino)-6-amino-1-oxohexyl]amino]-2-phenylethyl]hydroxyphosphinyl]- (9CI) (CA INDEX NAME)

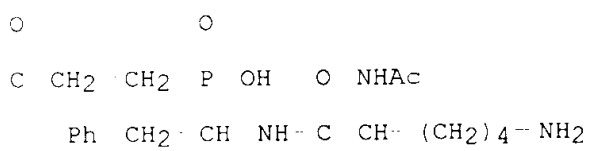


RN 181111-55-7 HCAPLUS
CN Phosphinic acid, (3-amino-3-oxopropyl)[1-[(2,6-diamino-1-oxohexyl)amino]-2-phenylethyl]- (9CI) (CA INDEX NAME)



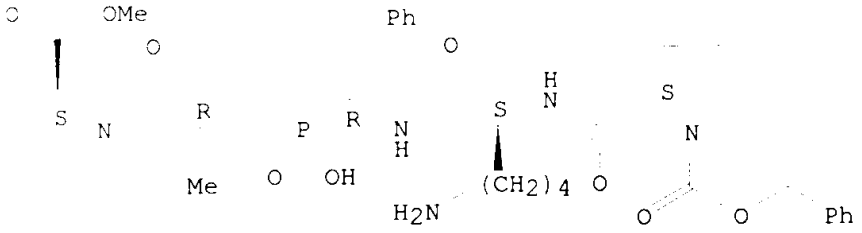
RN 181111-75-1 HCAPLUS

CN Phosphinic acid, [1-[[2-(acetylamino)-6-amino-1-oxohexyl]amino]-2-phenylethyl](3-amino-3-oxopropyl)- (9CI) (CA INDEX NAME)



L6 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:481069 HCAPLUS
DOCUMENT NUMBER: 125:161938
TITLE: Structure of astacin with a transition-state analog inhibitor
AUTHOR(S): Grams, Frank; Dive, Vincent; Yiotakis, Athanasios; Yiallouros, Irene; Vassiliou, Stamatia; Zwilling, Robert; Bode, Wolfram; Stoecker, Walter
CORPORATE SOURCE: Max-Planck-Inst. Biochem., Planegg-Martinsried, D-82152, Germany
SOURCE: Nature Structural Biology (1996), 3(8), 671-675
CODEN: NSBIEW; ISSN: 1072-8368
PUBLISHER: Nature Publishing Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The structure of the zinc peptidase astacin in complex with a phosphinic peptide suggests that a special role is played by the side chain of a zinc-bound tyrosine, which is shifted to form a hydrogen bond to the phosphinyl group-a mimic of the carboxyanion of the transition state.
IT **180156-46-1**
RL: PRP (Properties)
(complexes with astacin; structure of astacin with a transition-state analog inhibitor)
RN 180156-46-1 HCAPLUS
CN L-Proline, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2R)-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:368760 HCAPLUS
DOCUMENT NUMBER: 125:168620
TITLE: Highly potent and selective inhibitors of endothelin

converting enzyme

AUTHOR(S): Chackalamannil, Samuel; Chung, Shin; Stamford, Andrew W.; McKittrick, Brian A.; Wang, Yuguang; Tsai, Hsingan; Cleven, Renee; Fawzi, Ahmad; Czarniecki, Michael

CORPORATE SOURCE: Schering-Plough Res. Inst., Kenilworth, NJ, 07033, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(11), 1257-1260
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

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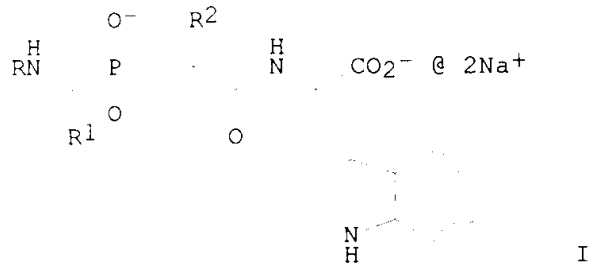


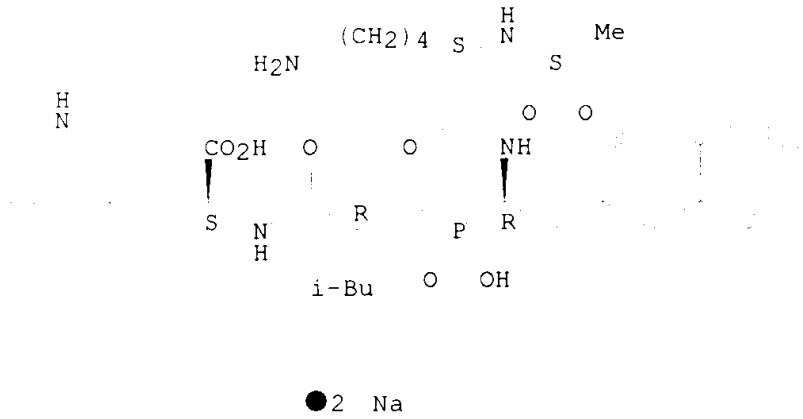
AB Phosphinic acid derivs. I [R = H, Z, Z-L-Leu, MeSO2-L-Lys, MeSO2-L-Lys(Z); R1 = 2-naphthylmethyl, PhCH2, Me2CHCH2; R2 = Me, CHMe2, CH2CHMe2; Z = PhCH2O2C] have been synthesized and evaluated as endothelin converting enzyme (ECE) inhibitors. Several of these compds., e.g. I [R = MeSO2-L-Lys, MeSO2-L-Lys(Z), R1 = 2-naphthylmethyl, R2 = CH2CHMe2; R = MeSO2-L-Lys(Z), R1 = R2 = CH2CHMe2], were potent inhibitors of ECE with a high degree of selectivity against neutral endopeptidase (NEP).

IT **180186-02-1P 180186-03-2P 180186-04-3P**
180186-05-4P 180186-28-1P 180186-29-2P
180186-30-5P 180186-31-6P 180186-32-7P
180186-33-8P 180321-08-8P 180321-09-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of peptide phosphinylmethylene analogs as highly potent and selective endothelin converting enzyme inhibitors)

RN 180186-02-1 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2R-(2R*,5R*,8S*)]- (9CI) (CA INDEX NAME)

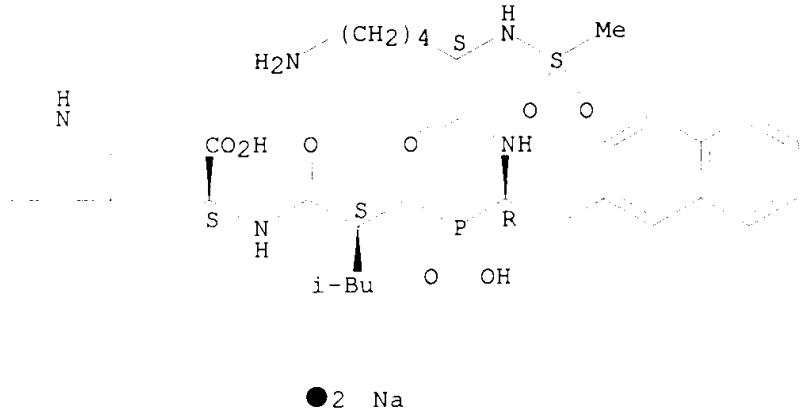
Absolute stereochemistry.



●2 Na

RN 180186-03-2 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5S*,8R*)]- (9CI) (CA INDEX NAME)

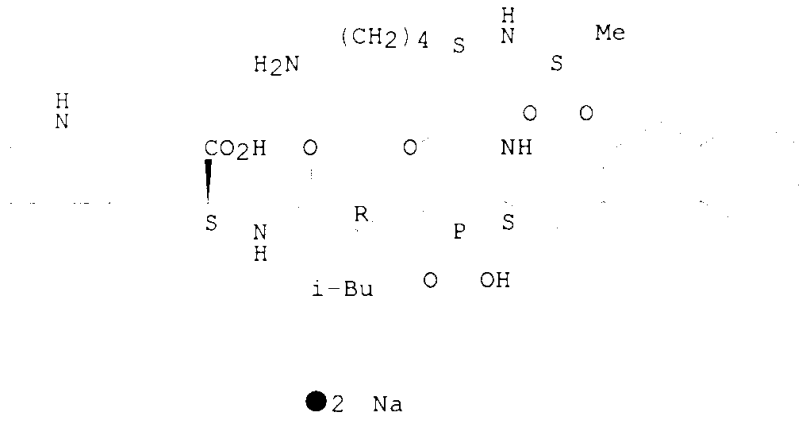
Absolute stereochemistry.



●2 Na

RN 180186-04-3 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2R-(2R*,5S*,8S*)]- (9CI) (CA INDEX NAME)

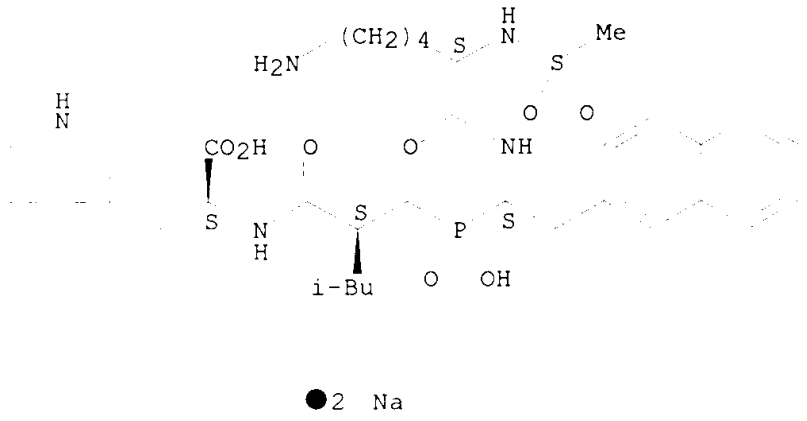
Absolute stereochemistry.



●2 Na

RN 180186-05-4 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5R*,8R*)]- (9CI) (CA INDEX NAME)

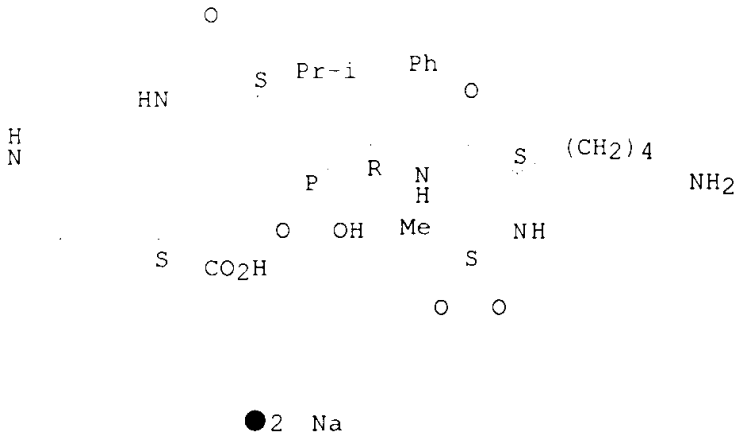
Absolute stereochemistry.



●2 Na

RN 180186-28-1 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5S*,8R*)]- (9CI) (CA INDEX NAME)

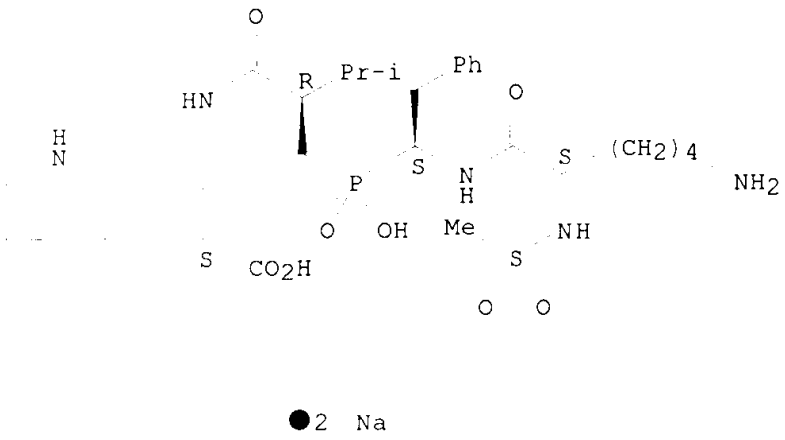
Absolute stereochemistry.



●2 Na

RN 180186-29-2 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2R-(2R*,5S*,8S*)]- (9CI) (CA INDEX NAME)

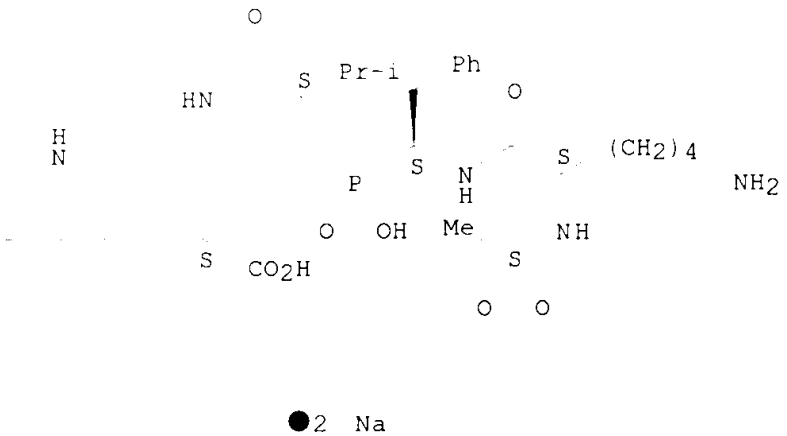
Absolute stereochemistry.



●2 Na

RN 180186-30-5 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5R*,8R*)]- (9CI) (CA INDEX NAME)

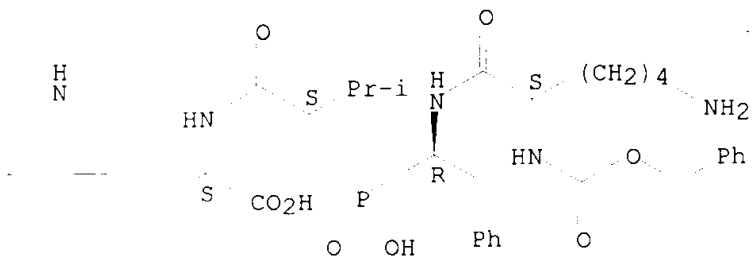
Absolute stereochemistry.



●2 Na

RN 180186-31-6 HCAPLUS
CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide, disodium salt, [3S-(3R*,6S*,9R*,12R*)]- (9CI) (CA INDEX NAME)

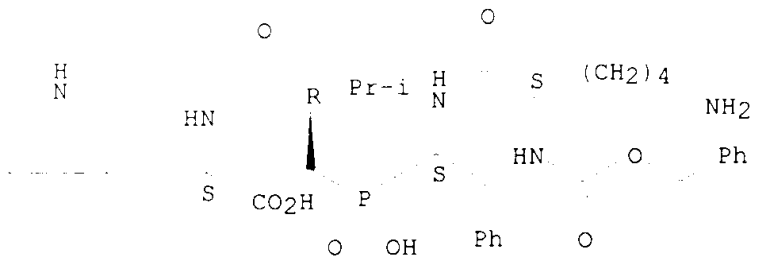
Absolute stereochemistry.



●2 Na

RN 180186-32-7 HCAPLUS
CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide, disodium salt, [3S-(3R*,6R*,9S*,12R*)]- (9CI) (CA INDEX NAME)

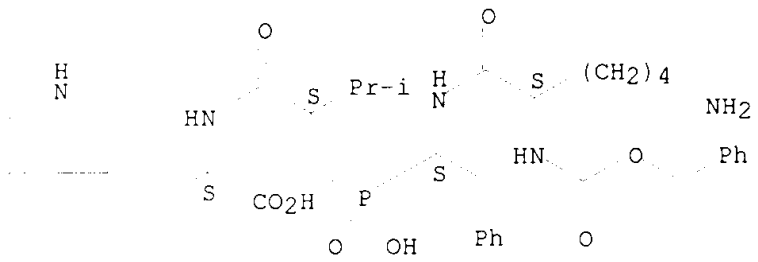
Absolute stereochemistry.



●2 Na

RN 180186-33-8 HCAPLUS
CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide, disodium salt, [3S-(3R*,6R*,9R*,12R*)]- (9CI) (CA INDEX NAME)

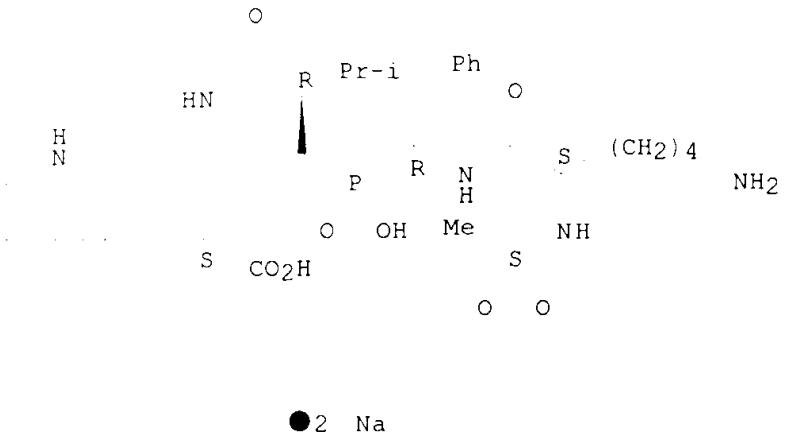
Absolute stereochemistry.



●2 Na

RN 180321-08-8 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

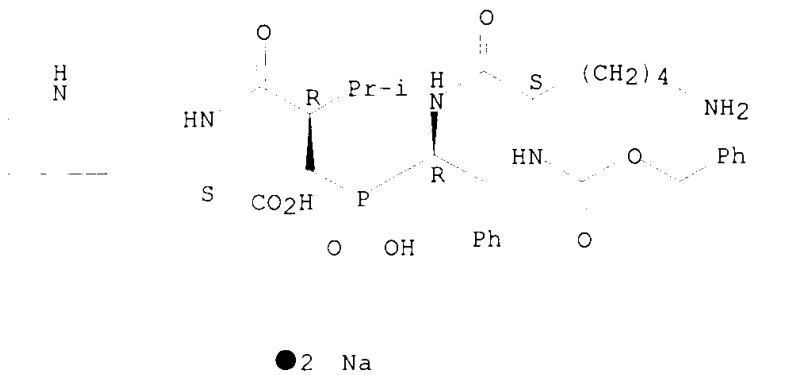
Absolute stereochemistry.



●2 Na

RN 180321-09-9 HCAPLUS
CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide, disodium salt, [3S-(3R*,6S*,9S*,12R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

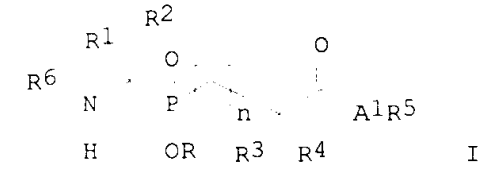
L6 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:50687 HCAPLUS
DOCUMENT NUMBER: 124:261746
TITLE: Amino acid phosphinic acid derivatives useful as endothelin converting enzyme inhibitors
INVENTOR(S): McKittrick, Brian A.; Czarniecki, Michael F.; Chackalamannil, Samuel; Chung, Shin; Defrees, Shawn; Stamford, Andrew W.
PATENT ASSIGNEE(S): Schering Corp., USA
SOURCE: U.S., 34 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5476847	A	19951219	US 1994-267630	19940629
CA 2191454	AA	19960111	CA 1995-2191454	19950619
WO 9600732	A1	19960111	WO 1995-US7128	19950619
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9529013	A1	19960125	AU 1995-29013	19950619
EP 767794	A1	19970416	EP 1995-924573	19950619
EP 767794	B1	20000202		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10502081	T2	19980224	JP 1995-503179	19950619
AT 189455	E	20000215	AT 1995-924573	19950619
ES 2144131	T3	20000601	ES 1995-924573	19950619

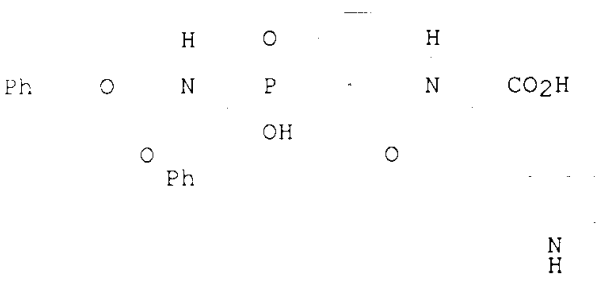
PRIORITY APPLN. INFO.: US 1994-267630 A 19940629
WO 1995-US7128 W 19950619

OTHER SOURCE(S): MARPAT 124:261746

GI



I



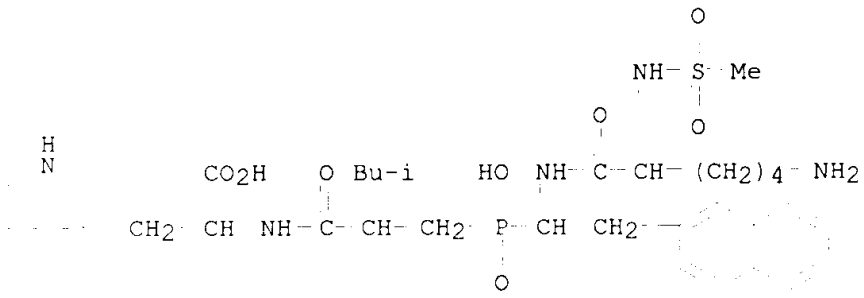
II

AB Phosphinic acid derivs. I or a pharmaceutically acceptable salt thereof, wherein R is H, alkyl or alkanoyloxymethylene; R1, R2, R3 and R4 are H, alkyl, alkenyl, alkenylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, carboxyalkyl, thioalkyl, alkoxythioalkyl, aminoalkyl, alkylaminoalkyl, cycloalkyl-substituted alkyl or heterocycloalkyl; or R1 and R2 form a cycloalkyl ring of 3-8 members and R3 and R4 are as defined; or R3 and R4 form a cycloalkyl ring of 3-7 members and R1 and R2 are as defined; or R1 and R2 together, and R3 and R4 together, each form a cycloalkyl ring; R5 is OR9 or NHR9, wherein R9 is hydrogen or alkyl; n is 0 or 1; A1 is p-aminobenzoyl or p-aminobenzenesulfonyl, or A1 and R5 together form a radical of an

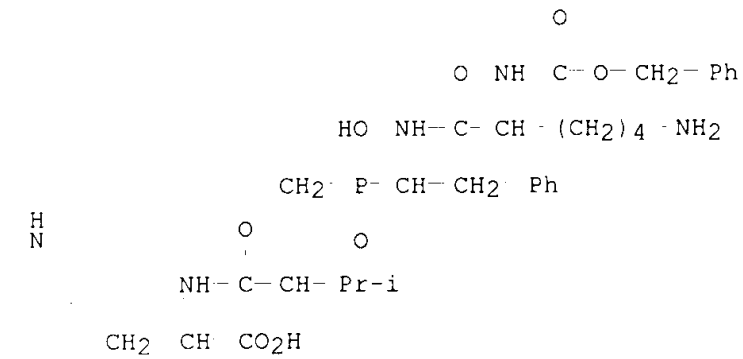
.alpha.-aminoacyl deriv.; and R6 is phenylmethoxycarbonyl, arylcarbonyl, heteroarylcarbonyl or A2R7, wherein A2 is a divalent .alpha.-aminoacyl radical, and R7 is a substituent on the .alpha.-amino atom selected from H, R8OCO, R8SO2 and R8NHCO, wherein R8 is aryl, arylmethyl or (C1-C8) alkyl; are disclosed for use as endothelin converting enzyme inhibitors; also disclosed are a genus of novel compds. wherein R3 and R4 form a cycloalkyl ring. Thus, e.g., Me ester II (prepn. given) was sapond. to the carboxylic acid which exhibited endothelin converting enzyme inhibiting activity of IC50 = 190 nM. Pharmaceutical formulations were given.

IT **174768-21-9P 174768-27-5P 174768-34-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid phosphinic acid derivs. useful as endothelin converting enzyme inhibitors)

RN 174768-21-9 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]- (9CI) (CA INDEX NAME)



RN 174768-27-5 HCAPLUS
CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide (9CI) (CA INDEX NAME)



RN 174768-34-4 HCAPLUS
CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-

trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-
(9CI) (CA INDEX NAME)